REMARKS

Entry of this Amendment is proper under 37 C.F.R. § 1.116, because the Amendment places the application in condition for allowance for the reasons discussed herein; does not introduce any new claims; does not raise any new issue requiring further search and/or consideration because the amendments amplify issues previously discussed throughout prosecution, and places the application in better form for an appeal should an appeal be necessary.

As set forth in the Office Action Summary, claims 33-57 are pending. Claim 33 is amended herein. Basis for the amendment may be found throughout the specification and claims as-filed, especially at page 3, lines 17-20 and Figures 1-6.

Objections

Claims 54 and 57 stand objected to, as the Office alleges that "a claim, which depends from a dependent claim, should not be separated by any dependent claim, which does not also depend from said dependent claim". (Office Action, page 2). The Office cites to MPEP § 608.01(n). Applicants note that the referenced section of the MPEP is directed to multiple dependent claims; however, claims 54 and 57 are not multiple dependent claims.

With regard to the order of the present dependent claims, Applicants note that the dependent claims only depend from earlier claims; therefore, Applicants respectfully submit that the claim order is appropriate. Applicants further respectfully submit that if the Office deems it to be appropriate, the Office can renumber claims upon allowance. Thus, if Applicants have not addressed the Office's concern, clarification with regard to this objection is requested.

Rejections Under 35 U.S.C. § 112, first paragraph

Claims 33-44 stand rejected under 35 U.S.C. § 112, first paragraph, as purportedly failing to comply with the written description requirement. The Office argues that the original specification does not describe a synergistic effect.

In the interest of expediting the prosecution, and without acquiescing in the rejection, independent claim 33 is amended herein to recite "said IL-2 and MIP chemokine are both expressed in said tumor so as to provide an improved anti-tumor response in said patient when compared to the anti-tumor response in said patient administered with a composition comprising a vector comprising only the nucleic acid sequence (i) or the nucleic acid sequence (ii)", thus removing the reference to a synergistic effect.

In light of the above amendment to claim 33, Applicants submit that the specification does support the concept that the present method provides an improved anti-tumor response, as compared to methods using a single component composition. The specification at page 3, lines 17-20 refers to "improved properties of said constituents", thus disclosing the greater anti-tumor response generated by the composition associating IL-2 with a MIP chemokine as compared to the IL-2 or MIP taken independently.

Applicants refer to the working examples, as further illustrating the anti-tumor response provided by compositions expressing both IL-2 and a MIP chemokines. Three different tumor models are set forth: B16F0 (Figures 1 and 2), RENCA (Figures 3 and 4) and P815 (Figures 5 and 6), as compared to the anti-tumor response observed with individual vector encoding IL-2, MIP-1a or MIP-1b.

As further shown in Figure 1, direct intratumoral injection of adenoviral vectors expressing both MIP-1a and human IL-2 into subcutaneous B16F0 melanoma tumors in mice significantly slowed tumor progression more effectively than treatment with adenoviral vectors expressing either human IL-2 or MIP-1 alpha. In addition, survival was enhanced in the group treated using the method of the invention, as compared to the groups treated with vectors expressing either human IL-2 or MIP-1 alpha (50% survival 30 days post therapy termination versus 15 days following administration of an empty Ad control and Ad-MIP-1 alpha and approximately 22 days following injection of Ad-IL-2 (Figure 2)).

RENCA tumor development was also delayed in mice treated with nucleic acid sequences encoding both IL-2 and MIP-1 beta (resulting in a stabilization of tumor burden more than 25 days post injection). In contrast, mice treated with nucleic acid sequences encoding development was observed in mice treated with nucleic acid sequences encoding MIP-1 beta alone. The measurement of the survival rate shown in Figure 4 also supports this point. 50% of the mice treated with acid nucleic sequences encoding only MIP-1 beta were alive at day 27, 50% of the mice treated with acid nucleic sequences encoding IL-2 were alive at day 43, but 50% of the mice treated with acid nucleic sequences encoding both MIP-1 beta and IL-2 were still alive at day 52. 36% of mice survived for more than 100 days after being treated with IL-2 and MIP-1 beta in combination. The proportion of surviving mice was greatly reduced following treatment with IL-2 alone and null following treatment with MIP-1 beta alone (all of these mice died within a period of 41 days).

The effective response against P815 tumors provided by the combination of a MIP chemokine and IL-2 is also shown in Figures 5 and 6. In this experiment, the

anti-tumor activity of the combination of MIP-1 alpha and IL-2 was compared to that provided by combination of IL-2 or MIP-1a with IFNg (a molecule known for having anti-tumor properties). As illustrated in Figure 5, tumor volume was significantly reduced in mice treated with nucleic acid sequences encoding both IL-2 and MIP-1 alpha, while continuous tumor development is observed in mice treated with nucleic acid sequences encoding IL-2 and IFNg and a rapid progression of tumor growth is seen in mice treated with nucleic acid sequences encoding MIP-1 alpha and IFNg. The survival rates of mice treated with MIP-1 alpha and IL-2 was enchanced as compared to other combinations. 67% of mice treated with the composition of the invention survived for more than 90 days post injection, whereas 50% of the mice treated with acid nucleic sequences encoding IL-2 and IFNg survived for 21 days, and 50% of the mice treated with acid nucleic sequences encoding both MIP-1 alpha and IFNg survived 27 days (with no tumor regression).

Thus, Applicants submit that the specification, including the working examples, provide support in the present claims for the concept that administration of nucleic acid sequences encoding both IL-2 and a MIP chemokine increases survival of animals having preexisting tumors, delays tumor growth and causes tumor regression in a significant proportion of the treated animals as compared to administration of nucleic acid sequences encoding either IL-2 or a MIP chemokine. Thus, the amendment to claim 33 is fully and reasonably supported by the specification as-filed.

Claim Rejections Under 35 U.S.C. 103(a)

Claims 45-47 and 49-50 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Boursnell *et al.* (US Patent 6,287,557) taken with Hobart *et al.* (US Patent 5,147,055), LaFace (US Patent 6,649,158) and Song *et al.* (*J.Exp.Med.*, 186:1247-1256, 1997). The Office argues that it would have been *prima facie* obvious to combine the teaching of Boursnell taken with Hobart and LaFace and Song to make and use a composition comprising a nucleotide sequence encoding IL-2 and a nucleotide sequence encoding an MIP1-beta to inhibit tumor growth in a patient, as well as to make such a composition. Applicants respectfully traverse.

As set forth in M.P.E.P 2142, in order to establish a *prima facie* case of obviousness, three criteria must be met, *i.e.*, (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings, (2) there must be a reasonable expectation of success, and (3) the prior art references must teach or suggest all the claim limitations. The cited references, alone or in combination, fail to satisfy these requirements for a case of obviousness.

Applicants submit that there is no motivation provided by the cited references to arrive at the claimed subject matter. None of the cited references contain an indication that a method associating IL-2 and MIP-encoding nucleic acid sequences would provide an effective anti-tumor response. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d

680, 16 USPQ2d 1430 (Fed. Cir. 1990). *See* also *In re Fritch*, 972 F.2d 1260, 23 USPQ2d 1780. Although the motivation need not be explicit, the motivation must be present to combine the prior art references in a manner to solve the problem. *See Ruiz v. A.B. Chance Co.*, 69 U.S.P.Q.2d 1686, 1690-91 (Fed. Cir. 2004).

Boursnell notes in passing that combinations of immunomodulating polypeptides such as cytokines and chemokines as well as complement components, immune system accessory/adhesion molecules and their respective receptors can be used for treating tumors. IL-2, MIP-1a and MIP-1b are cited as exemplary immunomodulating polypeptides along with more than 40 other immunomodulating polypeptides (*see* column 7, lines 1-14). However, Boursnell specifically refers to combinations of cytokines (*i.e.*, more than one cytokine) and combinations of cytokines and accessory/adhesion molecules (*see* column 7, lines 23-26), with further specific reference to combinations involving IL-2, GM-CSF, lymphotactin and/or CD40L (*see* column 8, lines 55-57).

Thus, Boursnell taken as a whole teaches that the specific selection of IL-2 and MIP1b (*i.e.*, the subject matter of the present invention) would represent 1 out of more than 780 possibilities. None of the examples are directed to such a combination. The references must be viewed as a whole for their teachings, and steps cannot be chosen and recombined with steps from another's teaching, in isolation of the teachings of the references as a whole. Boursnell illustrates the construction of HSV vectors expressing a single constituent), human GM-CSF or human IL-2. Boursnell's method is a prophetic, and is not entitled to a presumption of operability.

Hobart et al. disclose a method of treating solid tumors which relies on the sole administration of a plasmic DNA encoding IL-2 formulated with a cationic lipid mixture. However, there is no suggestion to combine the IL-2 encoding plasmid with a MIP-encoding nucleic acid sequence to improve the IL-2-mediated anti-tumor response. LaFace discloses that MIP-1 alpha is involved in the recruitment and chemotactic migration of immature dendritic cells to the tumor site (*see* page 17, lines 13-14). However, an efficient anti-tumor response requires differentiation and maturation in order to generate dendritic cells with highly developed antigen presentation functions.

In this context, LaFace discloses that GM-CSF and IL-4 are involved in the differentiation into immature dendritic cells and that further differentiation into mature dendritic cells can be induced by CD40 ligand, TNF alpha or LPS (*see* page 3, lines 25-28). Further, LaFace provides a method of inducting an anti-tumor response in a mammalian organism in which co-transduction of tumor cells with p53, GM-CSF, IL-4 and chemokines (*e.g.*, MIP-1 alpha) is done (*see* page 16, lines 24-26). Therefore, the skilled artisan would not have been motivated to associate a nucleic acid sequence encoding MIP-1 alpha with a nucleic acid sequence encoding IL-2. Instead, the reference teaches the skilled artisan to pursue the association of MIP-1 alpha with a cytokine such as IL-4 or GM-CSF in order to improve dendritic cells differentiation.

Song discloses the role of dendritic cells in the initiation of anti-tumor responses, and describes experimental work involving dendritic cells transduced with a recombinant adenovirus vector expressing a model antigen (beta-galactosidase). The last paragraph of Song proposes an approach based on the administration of

autologous dendritic cells transduced with an adenovirus vector encoding a relevant tumor antigen. Applicants note that IL-2 and MIP are not tumor antigens.

Therefore, the cited references contain no suggestion to combine the cited references to arrive at the claimed method, nor provide an expectation of success.

Claims 45, 50-54 and 57 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Boursnell taken with Hobart, LaFace and Song, and further in view of Bruder et al. (U.S. Patent No. 6,440,944). The Office argues that it would be *prima facie* obvious to make and use a replication defective adenoviral vector taught by Bruder in the method taught by Boursnell taken with Hobart, LaFace and Song.

Bruder et al. disclose a method relying on intramuscular administration of a recombinant adenovirus vector. Bruder teaches that the adenoviral vector is neutralized outside the muscle of administration (*see* column 4, lines 4-5), and that intra-muscular administration prevents leakage of the adenoviral vector from the target area and circumvents the humoral immune response elicited by the adenoviral vector (*see* column 2, lines 46-53). However, Bruder does not even suggest recombinant adenoviral vectors engineered to express both IL-2 and a MIP-1b chemokine.

In fact, Bruder teaches away from the method of the invention involving intratumoral administration. Therefore, the cited references, alone or in combination, fail to teach or suggest the claimed methods involving intratumoral administration of nucleic acid sequences encoding both IL-2 and a MIP chemokine, for providing anti-tumor response.

Claims 45, 55 and 56 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Boursnell taken with Hobart, LaFace and Song, and further in view of Gruber et al. (U.S. Patent No. 6,410,326). The Office argues it would have been *prima facie* obvious to make and use vaccinia virus taught by Gruber in the method taught by Boursnell taken with Hobart, LaFace and Song.

Gruber relates to recombinant retrovirus vectors. Gruber does not even suggest recombinant poxvirus vectors engineered to express both IL-2 and a MIP chemokine. Moreover, Gruber actually teaches away from the claimed method, because it discloses the drawbacks associated with the use of viral vectors based on DNA viruses such as adenovirus and vaccinia virus (*see* column 2, lines 16-40). Therefore, the cited references, alone or in combination, fail to teach or suggest the claimed methods involving administration of nucleic acid sequences encoding both IL-2 and a MIP-1b chemokine, for providing anti-tumor response.

Applicants request that the rejections under 35 U.S.C. § 103 be withdrawn.

CONCLUSION

From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully requested to telephone the undersigned so that prosecution of the application may be expedited.

Respectfully submitted,

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